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LEGAL DEPARTMENT
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EXAMINER
COOK, LISA V

ART UNIT	PAPER NUMBER
1641	

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14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/621,592	Applicant(s) JACKOWSKI, GEORGE	
	Examiner Lisa V. Cook	Art Unit 1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21,23-34 and 40-53* is/are pending in the application.

4a) Of the above claim(s) *40-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21 and 23-34* is/are rejected.

7)☒ Claim(s) *34* is/are objected to.

8)☒ Claim(s) *21,23-34 and 40-53* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Amendment Entry

1. Applicants' response to the Office Action mailed July 17, 2001 (Paper #12 filed 9/27/01 is acknowledged. In response to Amendment-C filed therein claims 35-39 were canceled, while new claims 40-53 have been added. In light of the newly submitted claims and further consideration, the following Restriction Requirement is required: Examiner apologizes for any inconvenience this may cause applicant.

Election/Restrictions

2. Restriction to one of the following inventions is required under 35 U.S.C. 121:

A. Group I - claims 21 and 23-34 are drawn to a method for the differential diagnosis of ischemic and hemorrhagic cerebral events, determining brain injury via the detection of either NSE, MBP, or S100, along with brain endothelial cell membrane protein, classified in class 435, subclass 7.92, for example.

B. Group II - claims 40-45, are drawn to a method for the determination of brain injury assessing presence and concentration of any two markers selected from brain endothelial cell membrane protein, NSE, MBP, or S100, classified in class 436, subclass 69, for example.

C. Group III - claims 41-53, are drawn to drawn to a method for the differential diagnosis of ischemic and hemorrhagic cerebral events, determining the level of four markers comprising NSE, MBP, or S100, along with brain endothelial cell membrane protein,, classified in class 514, subclass 12, for example.

3. The inventions are distinct, each from the other because of the following reasons:

Each of the method Groups A-C are distinct inventions because they have different modes of operation, different functions, or different effects. Specifically Group I involves the detection of brain endothelial cell membrane protein and one other marker, Group II involves the detection of any two of the recited markers, while Group III involves the detection of all four markers. Although the methods are directed to the detection of brain injury, they utilized variations from the same group of markers (i.e. myelin basic protein[MBP], beta isoform of S100 protein[S100], neuronal specific enolase[NSE], or brain endothelial cell membrane protein). Therein, the method to assess patient condition, analyzing different numbers of the patently distinct ischemic markers independently or in any combination thereof is directed to divers and independent markers of the recited method that require different procedural steps and different reagents. Therefore the methods differ in their modes of operation. Further, a search required for individual Group I, II, or III would not necessarily include a search for all of the methods. The search for one group is not totally and exclusively encompassed within the other groups.

4. Newly submitted claims 40-53 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: see Restriction as set forth above. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 40-53 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

OBJECTIONS WITHDRAWN

Priority

5. The instant application has now been amended to reference Canadian Application No. 2,263,063. Therein meeting the requirements for benefit of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78). The objection is withdrawn.

Specification

6. Applicants amendment to the specification has obviated the following objections:

I. In the instant application, the Brief Description of the Drawings is misleading. On page 6, lines 4 and 5 of the disclosure figures 3-10 are represented by one description which implies that each of the graphs are identical or have minimal differences so as to constitute their grouping. However, the figures are further described on pages 25 and 26 of the disclosure and taught to be substantially different-data from different patients exemplifying different events. It is recommended that the clarified descriptions on page 25-26 for each figure 3-10 be incorporated into section (g) Brief Description of the Drawings. See MPEP 608.01(f).

II. Also, the instant application appears to have several related applications/patents that were not incorporated into section (b) Cross-References to Related Applications. (i.e. USP#s: 5,744,358 - 5,747,274 – 5,604,105 – 5,710,008 –5,290,678 – Application #s: 08/026,453 – 08/481,743).

III. The use of several trademarks is noted in this application. They should be capitalized wherever they appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks. (For example, see page 14 – OPUS®, OPUS MAGNUM® etc).

OBJECTIONS MAINTAINED

Drawings

7. The formal drawings filed 3/30/01 in this application have been objected to by the Draftsperson under 37 CFR 1.84 or 1.152 (see PTO-948). Applicant is required to submit a proposed drawing correction in reply to this Office action. However, formal correction of the noted defect can be deferred until the application is allowed by the examiner.

Information Disclosure Statement

8. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the examiner on form PTO-892 or applicant on PTO-1449 has cited the references they have not been considered.

9. The information disclosure statement (form PTO-1449) filed in paper #5 in March 30, 2001 has been considered as to the merits.

Oath/Declaration

10. A new oath or declaration is required because it does not identify the post office address of each inventor. A post office address is an address at which an inventor customarily receives his or her mail and may be either a home or business address. The post office address should include the ZIP Code designation. The inventors' full address appears to be 17725 Keele St., Kettleby, Ontario, Canada L0G 1JC and this address has not been properly executed in the oath.

The wording of an oath or declaration cannot be amended. If the wording is not correct or if all of the required affirmations have not been made or if it has not been properly subscribed to, a new oath or declaration is required. The new oath or declaration must properly identify the application of which it is to form a part, preferably by application number and filing date in the body of the oath or declaration. See MPEP §§ 602.01 and 602.02. A new oath correcting the cited full and correct address of the invention has not been received, the objection is maintained.

NEW GROUNDS OF REJECTION NECESSITATED BY AMENDMENT

Claim Objections

11. Claim 34 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 34 necessitates the analysis of all four markers via steps 1-6. However claim 21 merely requires the detect ion of brain endothelial cell membrane and one other marker.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 21, 23-34 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 23 remains vague and indefinite in utilizing the phrase "blood components". Because the term is not defined in the disclosure the metes and bounds cannot be determined. Is it applicants' intent to claim any material containing blood, any product useful in blood analyses, or any product derived from blood? Please clarify.

B. In claim 28, the use of " a single same sample" remains vague and indefinite because it is unclear as to what is encompassed by the phrase. Is the "a single sample" wording directed to separate aliquots from the same sample wherein the reaction for each marker is separately analyzed or does a single sample refer to a single reaction wherein all the markers are added to a single sample? On page 16, line 1, of the specification, samples were centrifuged and aliquots of serum were frozen for further analyses. If applicant intends to claim same sample aliquots it is suggested that the claim language recite this to eliminate any ambiguity.

C. Claims 21 and 24 recite "combinations thereof". It is not clear as to what combinations are being claimed. It appears that any combination of any of the recited proteins or any additional composition containing any of the recited proteins would meet the limitation of this claim. No specific guidance was provided through a clear definition of what "combinations thereof" is meant to entail. Please explain.

D. Claims 26 and 27 are drawn to a method that requires a secondary marker which is "cell type specific with respect to" the other markers utilized in the method. This claim is vague and indefinite because it is not clear as to what "cell type specific with respect to" applicant is referring. It is suggested that applicant include the specific cell type to obviate this rejection.

E. New claim 34 is vague and indefinite because it appears to detect NSE, MBP, and S100. However it is dependent on claim 21 which merely requires that one of these proteins be detected. Please clarify.

12. Claims 21, 23-34 (specifically claims 21) remain rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. There are no claimed steps reciting the washing or removal of unbound materials. If no separation will be performed it is unclear how the complex will be identified from the reaction solution containing both bound ad unbound material. Further, there are no steps that identify reagent and sample contact thereby forming a detectable complex which is correlated to the diagnosing and distinguishing of stroke as recited in the preamble. Applicant has not addressed the rejection, it is therein maintained.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 21, 23-34 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. The methods of independent claim 21 have insufficient steps. These critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). Merely, reciting the use of reagents in an assay format is not considered a proper method step. An assay as recited in the preamble of claims 21, requires at least a contact step between reagent and sample – resulting in binding/complex formation, separation, detection, and a correlation step directed to the analysis of interest. The recited claims do not include the required steps for contact, formation, separation, detection and correlation. There are no claimed steps reciting the washing/removal of unbound material.

With respect to claims 21, a separation step that removes unbound reagents from the formed measurable complex is missing. If you do not have a separation step after complex formation, the addition of materials will always provide a positive result regardless of the amount of ligand bound to the antibodies in the formed complex and thus could not be utilized to detect the ligand or correlate it to an event. The presence of unbound materials is also a serious problem in view of the detection step, which is directed to quantitating the marker present in a sample as an indicator (diagnosing and distinguishing) of stroke.

The presence of the unbound materials will generate a greater detection signal as an indication of stroke than is actually present in the sample. Please add the removal of unbound label to the claims or clearly indicate the specific method of detection that does not employ the removal of unbound material. Applicant has not addressed the rejection, it is maintained.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 21, 23-34 remain rejected under 35 U.S.C.103(a) as being unpatentable over Jackowski (U.S. Patent # 5,604,105) or Jackowski (U.S. Patent # 5,710,008) in view of Strand et al. (Stroke, Dallas, 1984, 15(10, pages 138-44), Fassbender et al. (J. Neurol. Science, 1997, 148(1), pages 101-105), Huguet (Lyon Pharm, 1993, 44(3), pages 187-92-Abstract Only), Sulter et al. (Neurosci. Letters, 1988, 253(1) pages 71-73), or Yatsu et al. (Stroke, 1995, Vol.26, No.1, page 177).

Jackowski (5,604,105) teaches a method which detects a minimum of three markers that together present data distinguishing between ischemic and non-ischemic events. (Column 9, lines 64-67). A sample such as blood is contacted with antibodies specific for at least three markers to form a binding partner-marker binding pair. This complex is reacted with a second capture antibody to form a multiple antibody-marker composition. Each of the markers are then simultaneously assessed to ischemic events. (column 10, 17-62).

Jackowski (5,710,008) also disclose methods and kits to detect at least three different markers of ischemic disorders. In one embodiment the first marker is an ischemic marker, and the other two markers are specific for myocradial infarction. (column 20, lines 34-51). Several ischemic markers and their time of appearance in cardiac events is listed in Table 3.

Jackowski (5,604,105) and Jackowski(5,710,008) differ from the instant invention in not teaching the use of stroke specific markers as defined by claim 1, step a.

However, each of the recited markers (i-iv) are well known in the art and have been shown to correlated well with stroke events. This fact is supported by the following references:

Regarding, myelin basic protein, Strand et al. (Stroke) teach that myelin basic protein measurement is a good marker for predicting cerebral damage after stroke or cerebral hemorrhage (see abstract).

In the case of the S100 protein, Fassbender et al. (Journal of Neurol. Science) teach that serial quantification of S-100 in peripheral blood sample both acute and subacute phases of ischemic stroke is a significant measure of infarctions while control patient samples did not contain detectable S-100 (see abstract).

Neuron-Specific enloase (NSE) is disclosed by the reference of Huguet (Lyon Pharm.) as a significant tumor marker and possible indicator of neuronal damage in stroke patients (see abstract). Sulter et al. (Neurosci. Letters) also disclosed the utility of neuron specific enolase concentrations as a measure for ischemic stroke.

Lastly, Yatsu et al. (Stoke) identified Brain endothelial cells as an important protein in stroke measurements (see abstract).

Therefore, it would have been obvious at the time of applicants' invention to used known markers for stroke (namely, myelin basic protein, S100 protein, neuronal specific enolase, and brain endothelial cells as taught by Strand et al., Fassbender et al, Huguet et al., Sulter et al., or Yatsu et al. in either method of Jackowski (5,604,105) or Jackowski(5,710,008) because both methods of Jackowski teach that "many ischemic markers to which antibodies have been produce are well known in the art. (USP5,604,105-Column 2, lines 28-30).

One having ordinary skill in the art would have been motivated to do this because Jackowski (5,604,105) and Jackowski(5,710,008) taught that their method was rapid, accurate, sensitive, and could distinguish an ischemic event. (USP5,604,105-Column 9, lines 44-62)

Response to Arguments

Applicant contends that the instant invention employing the combination of known markers to evaluate ischemic events is not obvious is not found persuasive because the claimed markers were all known in the prior art as stroke indicators. The mere combination of these markers to produce a more accurate assessment is not viewed as patentable considering the following:

I. No more than routine skill is involved in adjusting the amount of a component of the claimed process to suit a particular starting material in order to achieve the result taught in the prior art. *Ex parte Rasmussen (POBA 1959) 123 USPQ 498.* Changes in temperature, concentrations, or other process conditions of an old process do not impart patentablility unless the recited ranges are critical (they produce a new and unexpected result). *In re Aller et al. (CCPA 1955) 220 F2d 454, 105 USPQ 233.*

II. A two step combination and two obvious process steps is unpatentable when each lends properties to the final product known to be produced when the step is practiced alone. In re Fortess (CCPA 1966) 369 F2d. 1009, 152 USPQ 13.

In response to applicant's arguments, the recitation "differential diagnosis of ischemic and hemorrhagic cerebral events" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., assessment via the use of an analytical flow chart set forth in claims 34-39) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

15. For reasons aforementioned, no claims are allowed.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 Fax number is (703) 308-4242 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (703) 305-0808. The examiner can normally be reached on Monday-Friday from 8:00 AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 305-3399.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Lisa V. Cook
Art Unit 1641
CM1-7B17
12/10/01